# Hypercalcemia of Malignancy
## Pathogenesis and Management

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# Disclosures

- Commercial Interests
  - None
- Off Label Usage
  - None

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# Objectives

- Discuss hypercalcemia of malignancy
  - Pathophysiology
    - Effect of cancer on bone remodeling
    - Consequences of hypercalcemia
  - Differential diagnosis
    - Cancer types causing hypercalcemia
  - Effect of antiresorptive therapy
    - On bone metastases and skeletal events
    - On hypercalcemia

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# Patient Scenario

- HPI: 23 year old woman with history of stage IV melanoma with metastases to the lung and bones
  - Refractory to treatment
  - Presented to Oncology service with altered mental status
- Labs:
  - Total calcium 15 mg/dL
  - PTH 4.0 pg/mL

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# Malignancy Associated Hypercalcemia (MAHC)

- Accounts for 90% of hypercalcemia in hospitalized patients
- Three main types
  - Humoral hypercalcemia of malignancy (HHM)
  - Local osteolytic hypercalcemia (LOH)
  - 1,25-dihydroxyvitamin-D induced hypercalcemia

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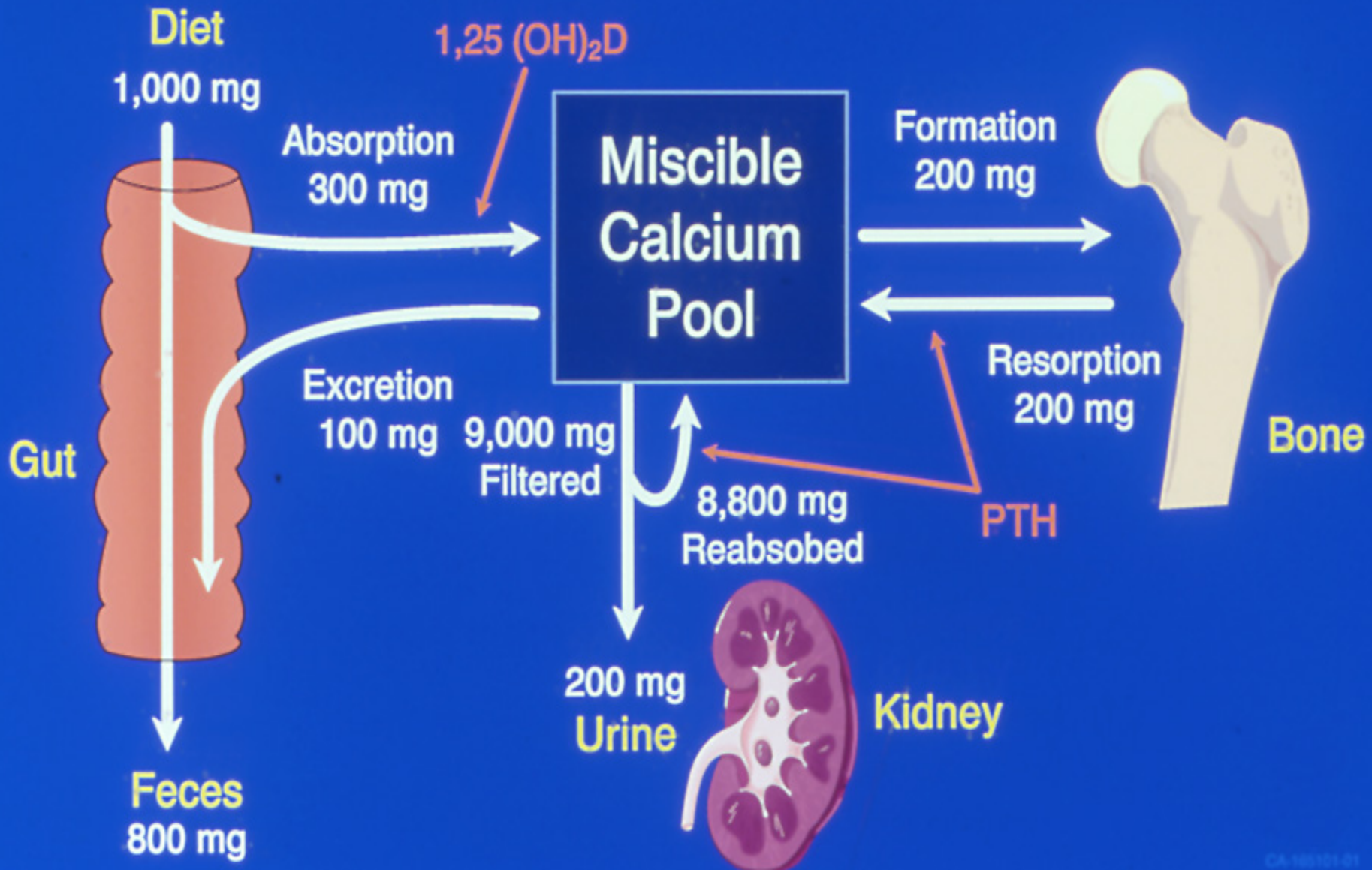
# DAILY CALCIUM FLUXES



# Malignancy Associated Hypercalcemia

## HHM – humoral hypercalcemia of malignancy

- Most common form of MAHC (~80%)
  - Cancer types: squamous (head/neck, esophagus lung, cervix), breast, kidney, bladder, ovary
- Mechanism: PTHrP secretion from tumor cells
  - Uncoupling of bone remodeling (unlike PHPT)
    - (+) Activates RANKL-osteoclast bone resorption
    - (-) Suppresses osteoblastic bone formation
  - Bone scans often (-) due to humoral mechanism
  - PTHrP has anti-calciuric effect to restrict urine calcium excretion

HHM=humoral hypercalcemia of malignancy. MAHC=malignancy associated hypercalcemia. PTHrP=parathyroid hormone related peptide. PHPT=primary hyperparathyroidism. RANK(L)=receptor activator of nuclear factor kappa-B (ligand)

# Malignancy Associated Hypercalcemia

## LOH – local osteolytic hypercalcemia

- Less common form of MAHC (~20%)
  - Cancer types: breast & hematologic (myeloma, lymphoma, leukemia) cancers
  - Poor prognosis
- Mechanism: cytokine mediated bone resorption
  - OAF's (IL's, TNF's, prostaglandins, lymphotoxin) ↑ RANKL and ↓ osteoprotegerin production
  - Bone scan results
    - Solid tumors often intensely (+)
    - Hematologic tumors may be (-), indicating reduced bone formation

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LOC=local osteolytic hypercalcemia. RANK(L)=receptor activator of nuclear factor kappa-B (ligand). OAF=osteoclast activating factor. IL=interleukin. TNF=tumor necrosis factor.

# Normal Bone Remodeling

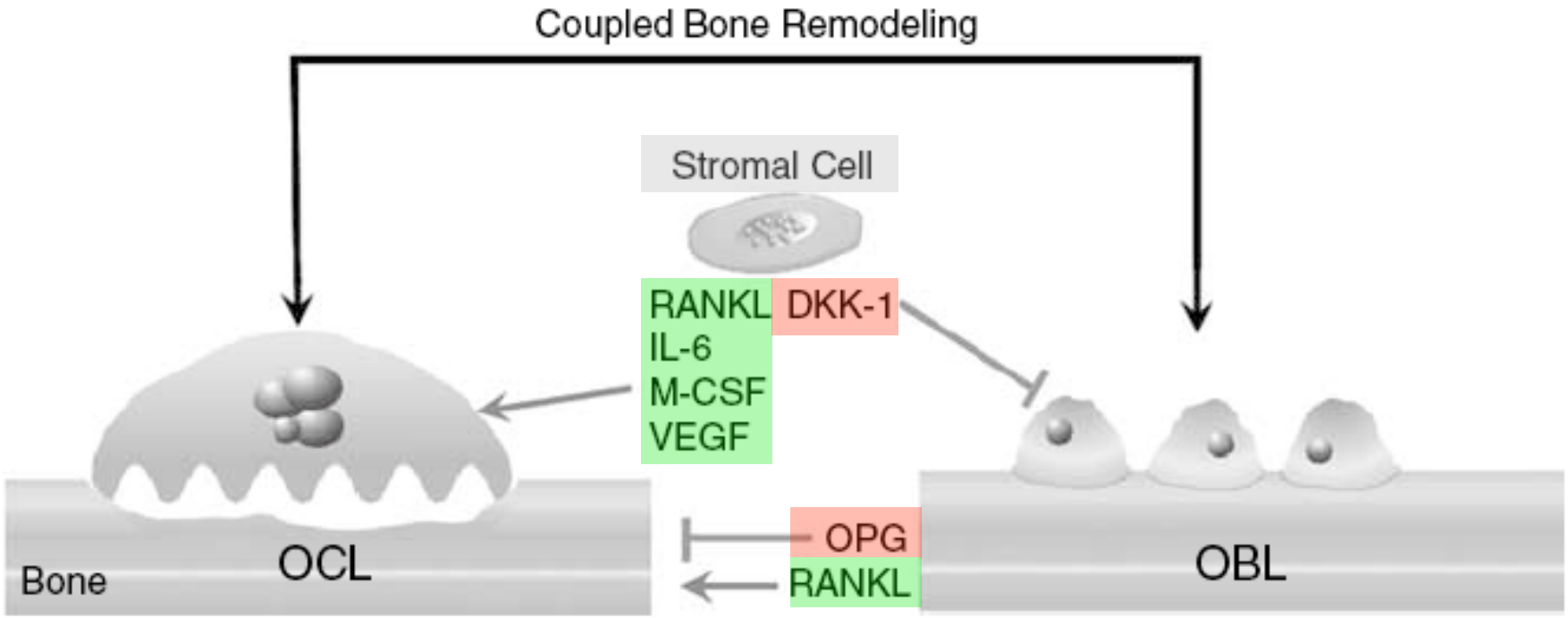



**Fig. 84.1.** Balanced physiologic bone remodeling. Physiologic bone remodeling is marked by balanced interactions between osteoclasts (OCL) and osteoblasts (OBL) within the bone marrow microenvironment. Locally produced cytokines and systemic hormones regulate the formation and activation of OCL. Systemic hormones (not pictured) stimulate OCL formation by inducing the expression of receptor activator of nuclear factor-κB ligand (RANKL) on marrow stromal cells and OBL. Stromal cells also produce OCL-stimulating factors including interleukin-6, macrophage colony-stimulating factor (M-CSF) and vascular endothelial growth factor (VEGF) that induce OCL formation. In addition, stromal cells produce dickkopf (DKK)-1, an OBL inhibitory factor. Coupling factors produced by OCL such as ephrins (not shown), also drive OBL differentiation while suppressing further OCL formation and activity. OBLs produce osteoprotegerin (OPG), a soluble RANKL inhibitor. Under physiologic conditions, OBL and OCL activity is balanced, in part due to the OPG/RANKL ratio. In myeloma bone disease, osteoclastogenesis is favored and osteoblastogenesis is inhibited.



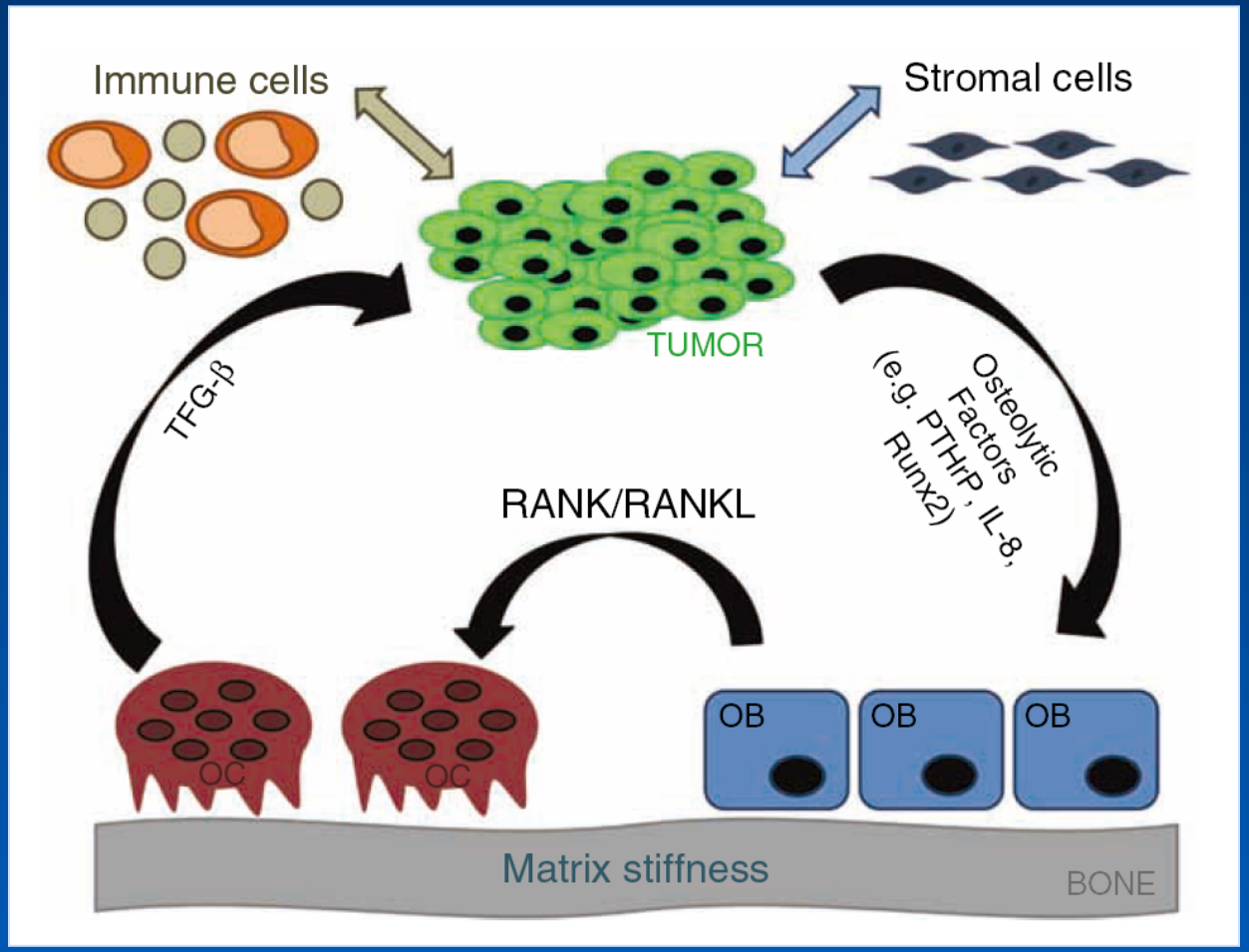
# Bone Metastases

## "Vicious cycle" of tumor & bone microenvironment

**Vicious Cycle[1]**

1. Tumor factors stimulate OC-mediated bone destruction
2. Growth factors are released from bone that further stimulate growth of tumor cells
3. Leads to tumor cell production of more tumor-derived osteolytic factors

Inhibiting OC-bone resorption **reduces tumor burden[2]** indirectly, & possibly by **inhibiting tumor factors** directly[3]




RANK(L)=Receptor Activator of Nuclear factor-Kappa-ß (Ligand). [1]Cancer 1997;80;1546. [2]Curr Opin Oncol 2011;23:338. [3]J Clin Invest 2002;110:1559. [3]J Clin Invest 1996;98:1544.

# Malignancy Associated Hypercalcemia
## Lymphoma (1,25-dihydroxyvitamin D mediated)

- Uncommon form of MAHC
  - 5-10% of patients with Hodgkin's disease
- Mechanism: Tumor cells (or adjacent cells) over-express 1-α-hydroxylase, producing 1,25-$(OH)_2D$
  - Generally, not a resorptive hypercalcemia
  - 1,25-dihydroxyvitamin D ↑ in (a) blood (b) tissue; levels may be discrepant from blood levels
    - (a) GI-absorptive hypercalcemia
    - (b) Activates RANKL osteoclastic hypercalcemia
  - Dehydration from hypercalcemia may ↓ renal clearance of calcium, worsening hypercalcemia

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RANK(L)=Receptor Activator of Nuclear factor-Kappa-ß (Ligand). LOC=local osteolytic hypercalcemia. MAHC=malignancy associated hypercalcemia. OAF=osteoclast activating factor.

 

# 1,25-di(OH)D-mediated Hypercalcemia
## Differential diagnosis

Granulomatous

- Acute granulomatous pneumonia
- Berylliosis
- Eosinophilic granuloma
- Pneumocystis carinii pneumonia
- Paraffin-induced
- Sarcoidosis
- Silicone-induced
- Wegener's

**Langerhans-cell histiocytosis**

**Nephrogenic systemic fibrosis**

**Infectious**

- Tuberculosis
- Candidiasis
- Leprosy
- Histoplasmosis
- Coccidioidomycosis
- Cat-scratch disease

**Malignant Lymphoproliferative disease**

- B-cell lymphoma (PTHrP)
- Hodgkin's disease (5-10% of patients)
- Lymphomatoid granulomatosis
- Dysgerminoma/seminoma
- Granulomatous slack skin

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# Skeletal Metastases

## Bone is often the 1st site of metastases

- Bone – the 3rd most common site for metastases
  - However, some common tumors (colon, prostate, oat cell, gastric) rarely cause hypercalcemia
- Breast cancer
  - Bone involved in 70% of patients with metastases
    - Often osteolytic (more commonly associated with pain, hypercalcemia, fracture)
- Prostate cancer
  - Bone involved in 90% of patients with metastases
    - Often osteoblastic

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# Skeletal Metastases

## Consequences of bone involvement

- Disordered bone remodeling
  - Osteo-blastic lesions
  - Osteo-lytic lesions (more common)
- Skeletal-related events
  - 4 major types: pathologic fractures, need for radiotherapy, need for surgery, and spinal cord compression
- Morbidity and mortality
  - Effects of surgery, radiation and chemotherapy
  - Symptoms of hypercalcemia
  - Bone pain

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# Skeletal metastases

## Consequences of hypercalcemia

- Gastrointestinal: smooth muscle effect (nausea, vomiting, constipation), ↑ gastric acid secretion (PUD), pancreatitis (?etiology)
- Renal: hypercalciuria (polyuria, renal stones), ↓ renal function
- CV: dehydration (hypotension)
- Musculoskeletal: abnormal bone remodeling (bone pain, bone loss + fractures, pathologic fractures)
- Neurologic: central nervous system (anorexia, anxiety, depression, cognitive dysfunction)

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LOC=local osteolytic hypercalcemia. MAHC=malignancy associated hypercalcemia. OAF=osteoclast activating factor. PUD=peptic ulcer disease.

 

# Evaluation

## NCCN task force guidelines for bone health[1]

- History – medication & fracture history, and FRAX®
- Physical examination
- Laboratory tests – as indicated; more extensive if hypercalcemia is present
- Radiology
  - Whole body bone scan (+) in osteoblastic lesions
  - Skeletal x-rays to evaluate pain & (+) bone scan
  - Bone mineral density (BMD)
    - BMD rate in breast cancer <20%[2]
    - BMD rate in prostate cancer at 0-1 year 10-20%[3]

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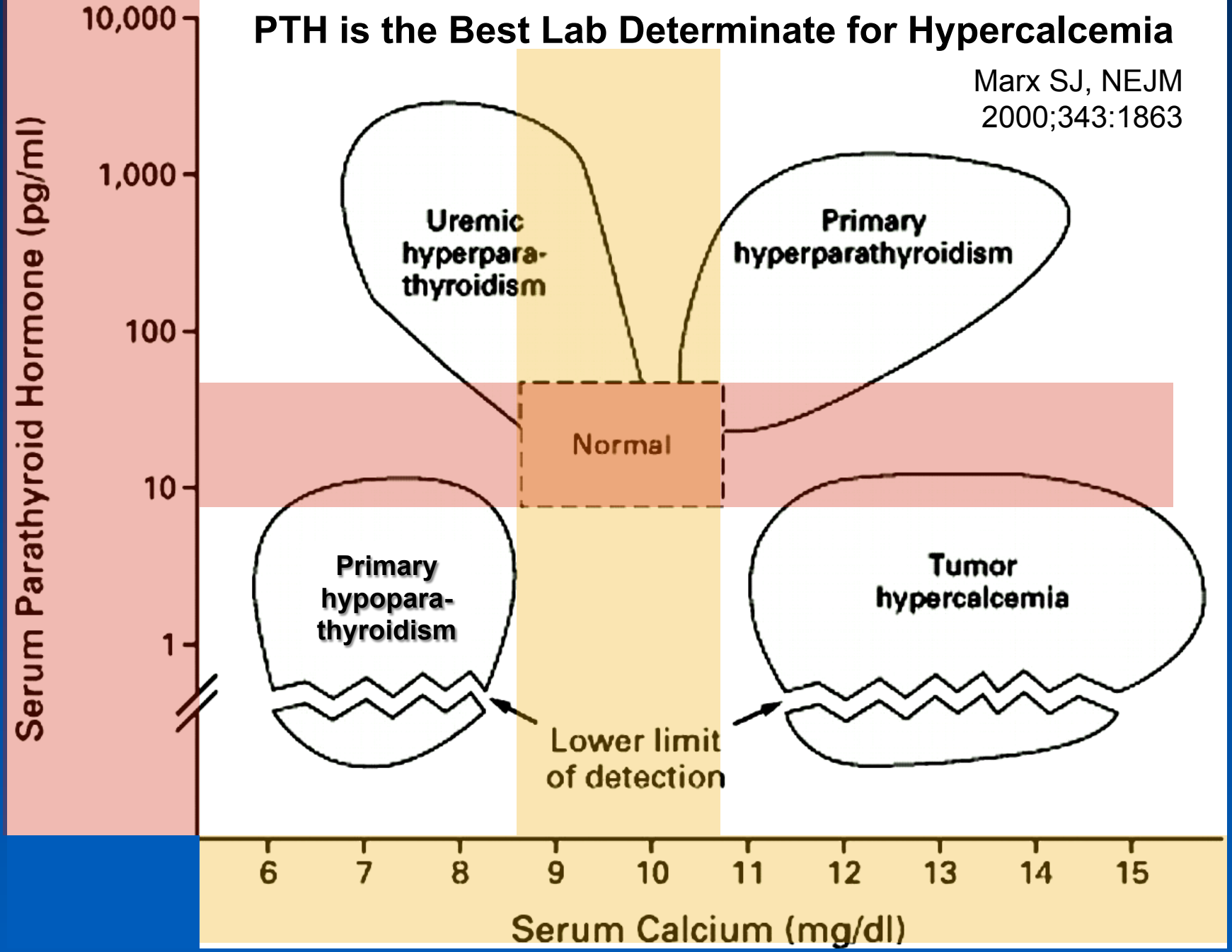
NCCN=National Comprehensive Cancer Network. [1]J Natl Compr Canc Netw 2013;11:S1. [2]J Clin Oncol 2009;27:1054. [3]Hosp Pract 2014;42:89.

# PTH is the Best Lab Determinate for Hypercalcemia

Marx SJ, NEJM 2000;343:1863



# PTH Suppressed Hypercalcemia
## Differential diagnosis

**Acute Renal Failure**
- AKI recovery phase
- Rhabdomyolysis-induced

**Granulomatous Disease**
- Sarcoidosis
- Coccidioidomycosis
- Histoplasmosis
- Leprosy
- Tuberculosis

**Immobilization**

**Malignancy**
- HHM (PTHrP mediated) ~80%
- LOC (OAF cytokine mediated) ~20%
- 1,25-di(OH)D ~uncommon

**Medications**
- Vitamin A toxicity (rare)
- Vitamin D toxicity (uncommon)
- Milk alkali syndrome (rare)
- Thiazide diuretic (common)

**Non-parathyroid endocrine disease**
- Adrenal insufficiency
- Hyperthyroidism
- Pheochromocytoma
- VIP-oma

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# Malignancy Associated Hypercalcemia
## Evaluation

- Is there any clinical evidence of cancer?
  - Laboratory tests
    - PTH + repeat calcium, phosphate, creatinine
    - CBC + differential, LFT, SPE
    - Alkaline phosphatase (AP) total + bone (BAP)
    - Tumor markers (PTHrP)
  - Radiographs
    - Chest radiograph and mammogram
    - Whole body bone scan (if ↑ AP or ↑ BAP)
      - Negative in osteolytic disease
    - Skeletal x-rays as indicated

LFT=liver function tests. CBC=complete blood count. PTH(rP)=parathyroid hormone (related peptide). SPE=serum protein electrophoresis.

# Hypercalcemia

## Lab values to establish the diagnosis of MAHC

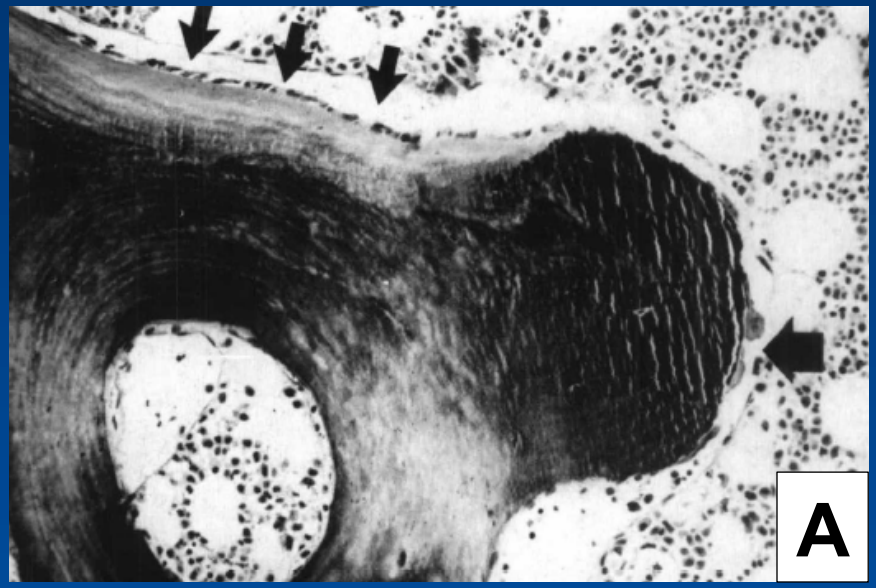
| Disease | $Ca^{+2}$ | Phos | PTH | PTHrP | $1,25(OH)_2D$ |
|---|---|---|---|---|---|
| **Primary HPT** | **High** | Low | **High** | Low | **High** |
| **Vitamin-D dependent** | **High** | **High** | Low | Low | **High** |
| **Humoral** (HHM) | **High** | Low | Low | **High** | Low (or NL) |
| **Osteolytic** (LOH) | **High** | NL | Low | Low | Low |

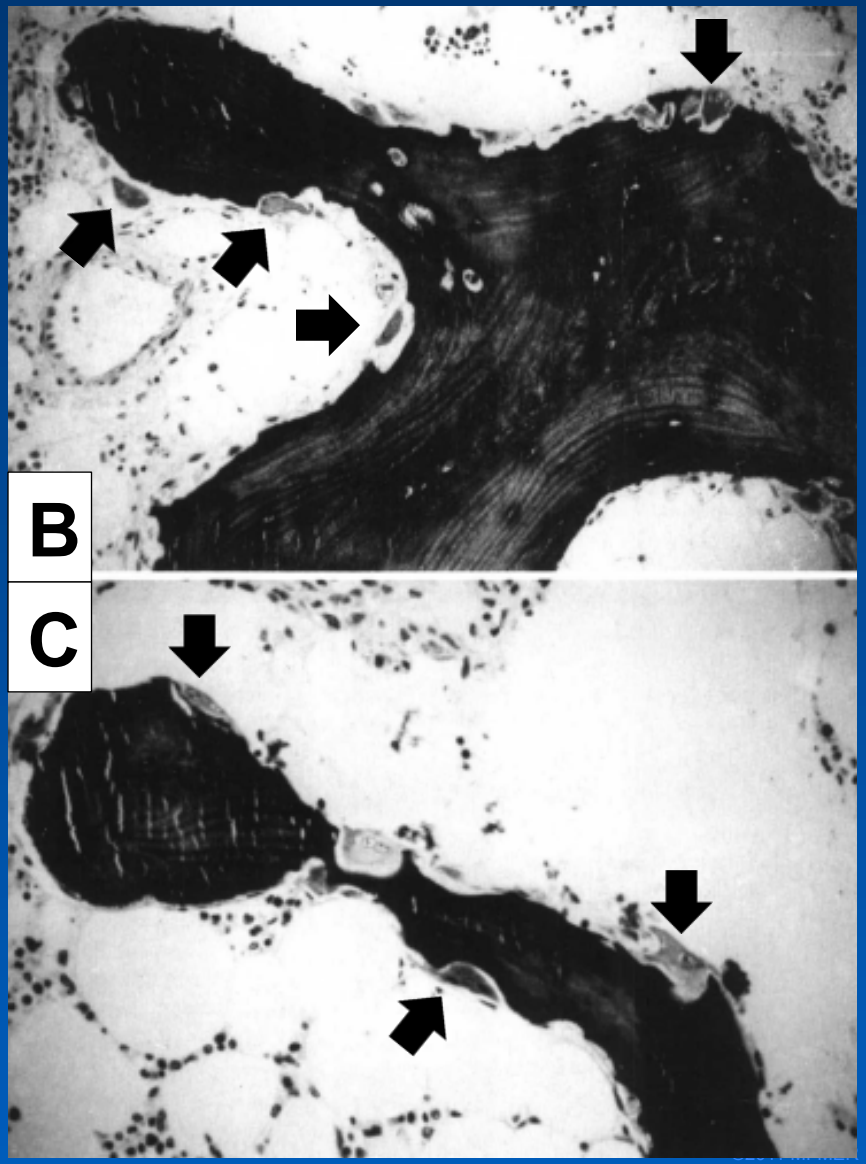
$Ca^{+2}$=calcium. Phos=phosphate. NL=normal. HHM=humoral hypercalcemia of malignancy. LOC=local osteolytic hypercalcemia. MAHC=malignancy associated hypercalcemia. PTHrP=parathyroid hormone related peptide. HPT=hyperparathyroidism.

# Bone Biopsy / Histomorphometry

## HPT and HHM bone remodeling




**Bone Histomorphometry**

**Fig A. (HPT) Primary Hyperparathyroidism**

- small arrows = osteoblasts
- large arrows = osteoclasts

**Fig B & C. (HHM) Humoral hypercalcemia of malignancy – uncoupled remodeling**

- marked ↑ in number of osteoclasts
- marked ↓ in osteoid / osteoblasts

J Clin End Metab 1982; 55:219

# Pathophysiology

## Metastatic bone involvement in ***breast*** cancer

- Dysregulation of normal bone remodeling
  - Both osteolytic & osteoblastic ↑ bone resorption[1]
    - Osteolytic with highest mean pain scores
- Breast cancer with the highest incidence of skeletal-related events[2-4]
  - Spinal cord compression 5-10%
  - Hypercalcemia 10-15%
  - Long-bone (pathologic) fractures 10-20%
  - Multiple vs solitary bone metastases
    - Solitary lesions associated with earlier stage, favorable histology, and better prognosis[5]

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[1]Br J Cancer 2000;82:858. [2]Clin Exp Metastasis 2007;24:169. [3]Br J Cancer 1987;55:61. [4]Clin Cancer Res 2006;12:6258s. [5]Breast Cancer Res Treat 2011;129:495.

 

# Pathophysiology

## Metastatic bone involvement in ***prostate*** cancer

- >90% local cancer stage at diagnosis; 5-yr DFS 100%
- Sites of bone metastases
  - Axial skeleton common, long bones less often
- Studies: skeletal-related events (SRE) in patients with ≥1 metastases, elevated PSA, and on ADT[1-3]
  - Pain is the most common symptom
  - SRE develop in 50% of patients within 2 yrs
    - Mean 1.5 events/yr, mean time to SRE 10.5 mos, and median survival 9.5 mos.
    - Pathologic fracture and need for radiation therapy were the two most common SRE

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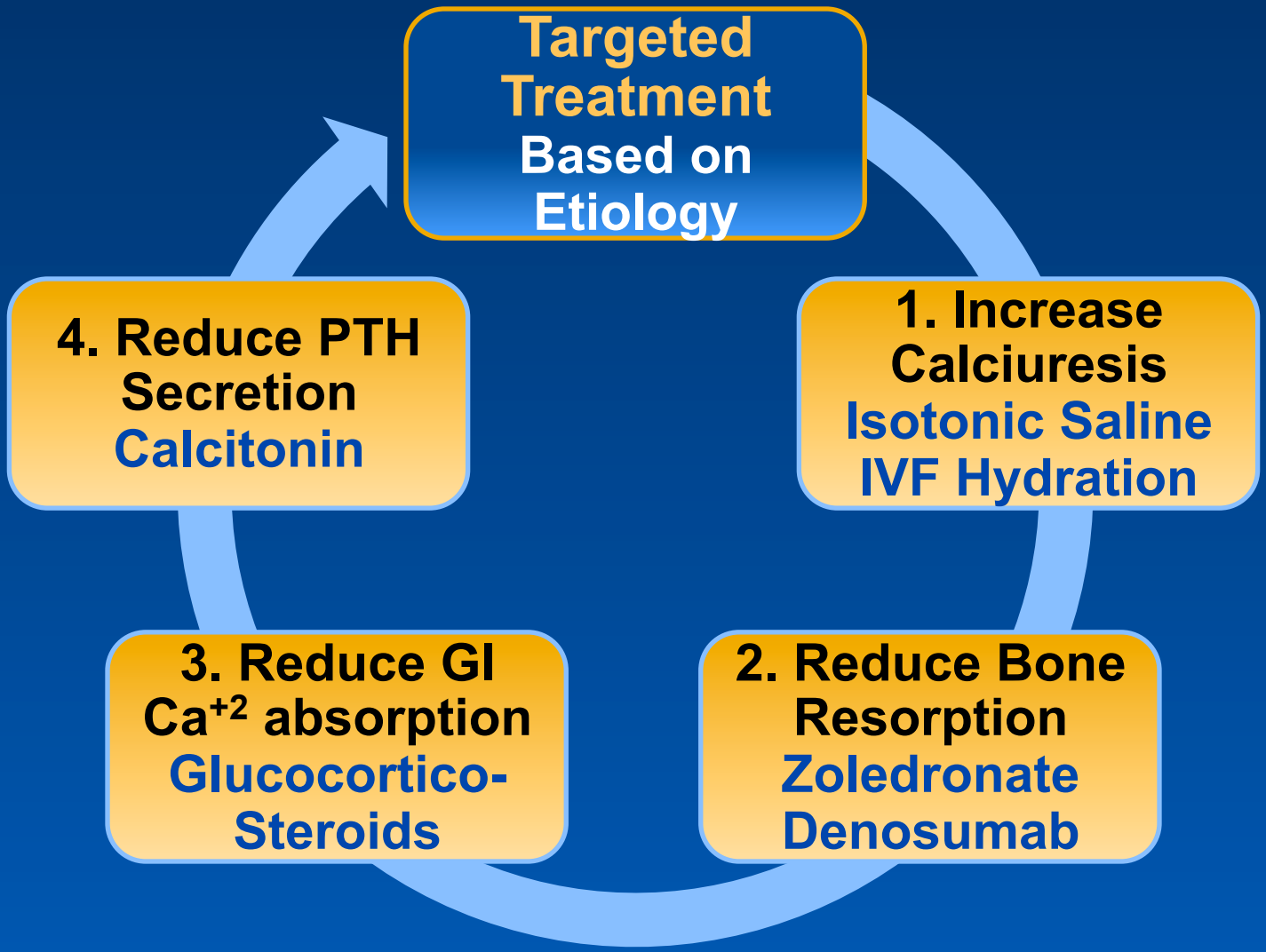
ADT=androgen deprivation therapy. DFS=disease free survival. [1]J Clin Oncol 2003;21:4277. [2]J Natl Cancer Inst 2002;94:1458. [3]J Natl Cancer Inst 2004;96:879. [4]Breast Cancer Res Treat 2011;129:495.


Targeted Treatment Based on Etiology
1. Increase Calciuresis
Isotonic Saline
IVF Hydration
2. Reduce Bone Resorption
Zoledronate
Denosumab
3. Reduce GI $Ca^{+2}$ absorption
Glucocortico-Steroids
4. Reduce PTH Secretion
Calcitonin



# Treatment of MAHC

## Standard therapy

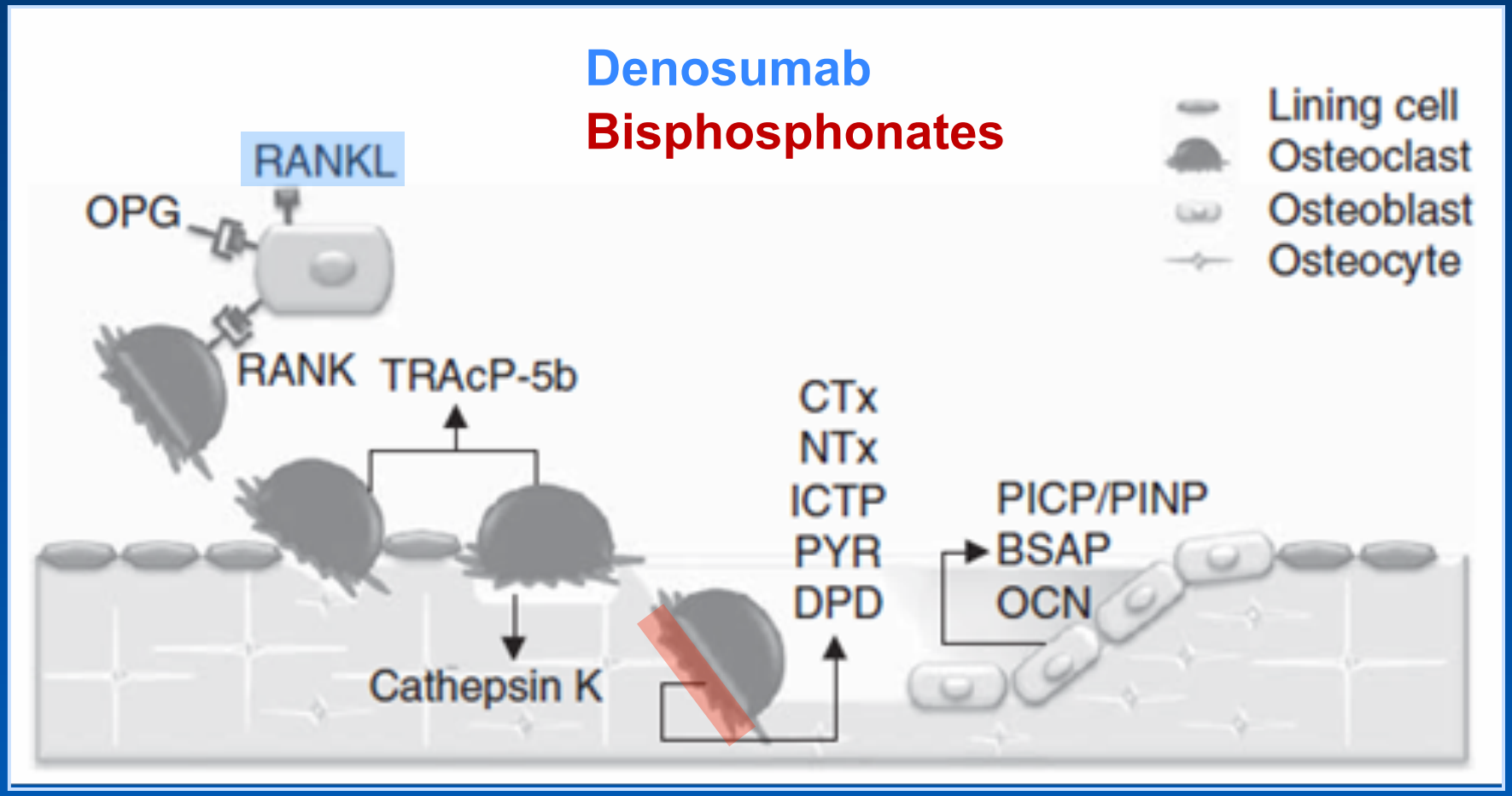
- IV fluid resuscitation / hydration
  - Saline – restore ECF space to euvolemia
    - Helps increase GFR, assists in calciuria
      - Lasix inhibits calcium reabsorption in renal thick ascending limb. Use loop diuretics if edema, cardiac dysfunction or if hyponatremia occurs
- Check and replace electrolytes, P, Mg as needed
- Parenteral antiresorptive therapy
  - Zoledronate (4-5 mg), pamidronate (60-90 mg)
    - Oral bisphosphonates not efficacious
  - Denosumab (60 mg)

MAHC=malignancy associated hypercalcemia. ECF=extracellular fluid. GFR=glomerular filtration rate. P=phosphate. Mg=magnesium.

# Bone Remodeling and Turnover Markers

Relation of BTM to origin of bone resorption or formation during bone remodeling



# Mechanism of Action of Bisphosphonates

## Osteoclasts are targets

Lining cells

Bisphosphonate

Osteoclast precursors

Osteoclast

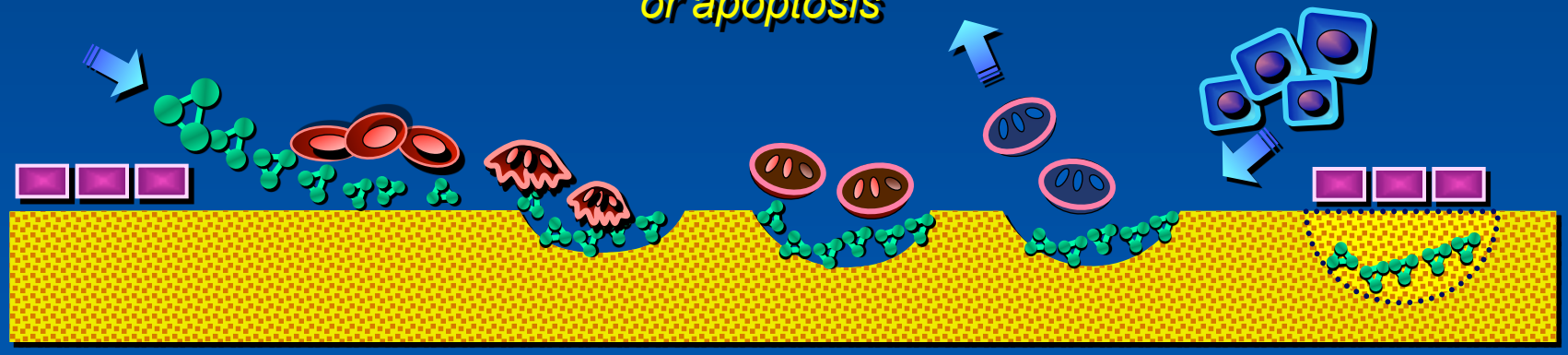
Inactivated osteoclast

Osteoblast

Bisphosphonate attaches to *exposed bone mineral* surfaces

Osteoclasts take up bisphosphonate → loss of ruffled border, *inactivation, detach and/or apoptosis*

New bone formation by osteoblasts renders bisphosphonate *inert when retained in bone*



J Clin Invest 1991;88:2095. Curr Med Res Opin 2004;20:1291. Osteoporos Int 2008;19:733.

# Treatment of MAHC

## Bisphosphonate therapy

- In the US, only zoledronic acid and pamidronate are approved to treat patients with bone metastases
  - Outside the US, ibandronate is approved for use
- Zoledronic acid (vs pamidronate)
  - More efficacious, but greater renal toxicity*
    - Onset of action 1-3 days, calcium nadir at 7-10 days
    - Response to therapy often 1-3 wks
  - Acute adverse effects
    - Nephrotoxicity (ATN); important to hydrate before use, and this may delay its use
    - Flu-like symptoms (cytokine mediated)

*Zoledronic acid associated with ATN (acute tubular necrosis, vs Pamidronate association with focal segmental glomerular sclerosis and nephrotic syndrome long-term. MAHC=malignancy associated hypercalcemia.

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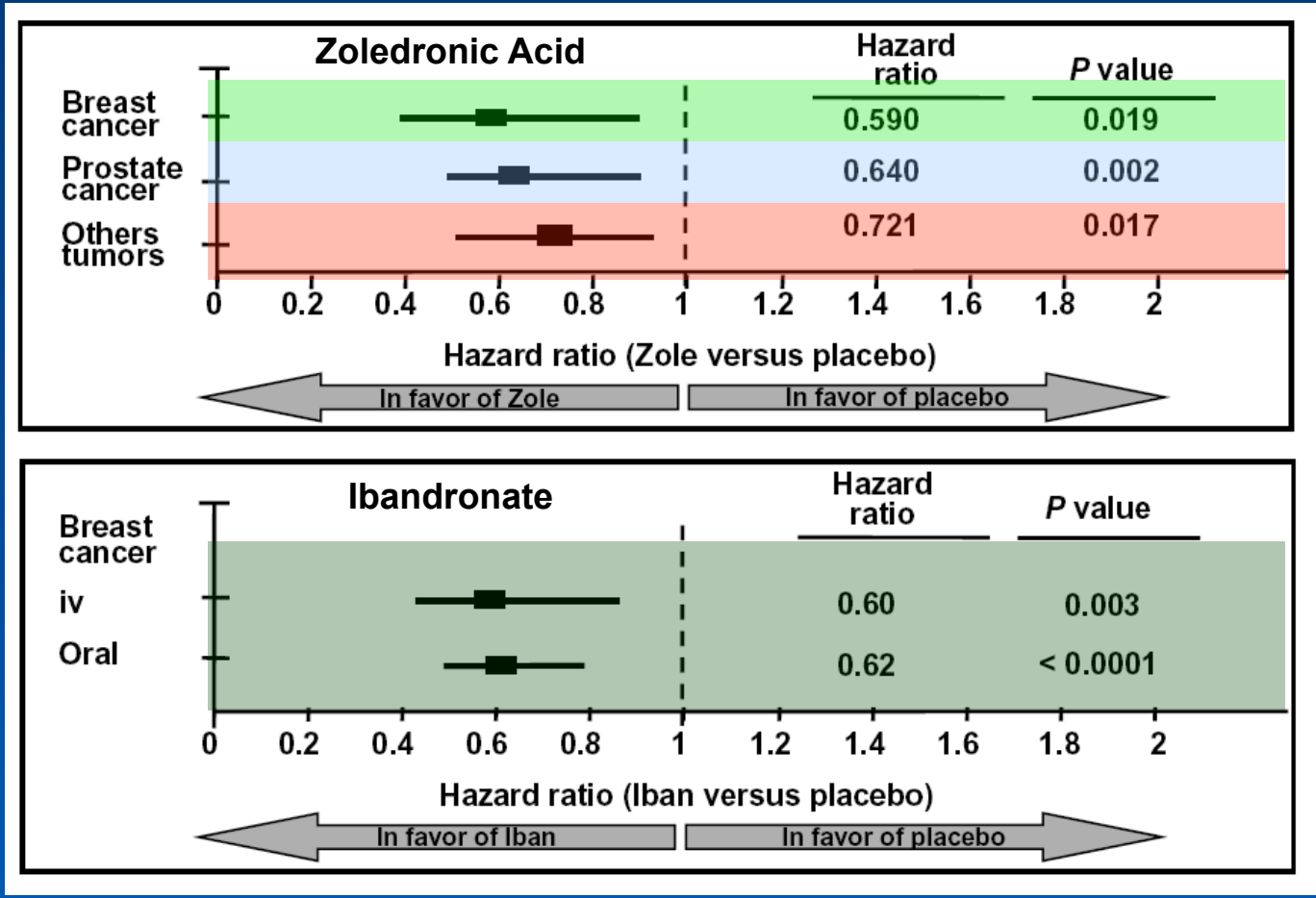
# Bone Metastases & Antiresorptive Therapy

## Risk of developing skeletal-related event

Patients with bone metastases; bisphosphonate therapy vs PBO




[1]Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 8th Ed. 2013.
PBO=placebo. Zole=zoledronic acid. Iban=ibandronate.

# Malignancy Associated Hypercalcemia
## Denosumab (Dmab) therapy

- Human monoclonal antibody (2014 US FDA approval for treatment of MAHC)
  - Binds RANKL
    - Prevents RANKL binding to RANK on osteoclasts, decreasing osteoclastic bone resorption
  - Dosing 120 mg subcutaneous q 4 wks
    - Calcium nadir at 9 days and extended response up to 3.5 months
    - Effective in bisphosphonate-refractory MAHC
  - Acute adverse effects
    - Hypocalcemia and hypophosphatemia
    - Musculoskeletal symptoms

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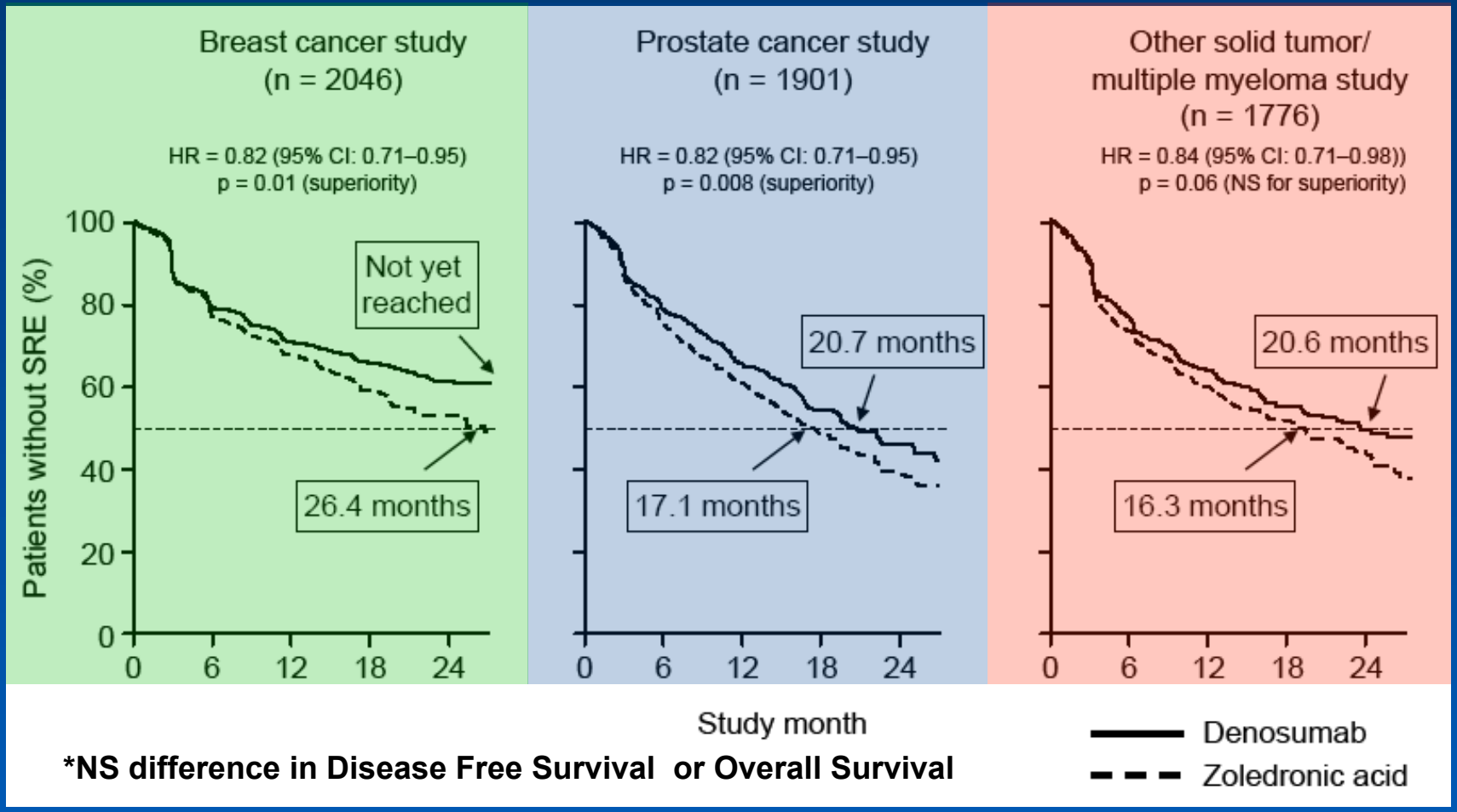
MACH=malignancy associated hypercalcemia. RANK(L)=receptor activator of nuclear factor kappa-B (ligand). FDA=food and drug administration.

# Metastatic Cancer & Antiresorptive Therapy

## Time to 1st skeletal-related event (SRE)*

Zoledronic acid vs Denosumab RCT[1] (Left: breast cancer metastatic to bone. Middle: Castrate resistant cancer with bone metastases)




***NS difference in Disease Free Survival or Overall Survival**

[1]Primer on the Metaabolic Bone Diseases and Disorders of Mineral Metabolism, 8th Ed. 2013. RCT=randomized controlled trial. [2]Lancet 2011;377:813. [3]J Clin Oncol 2010;28:5132.

# Metastatic Cancer & Antiresorptive Therapy
## Denosumab (Dmab) therapy vs bisphosphonates

- Dmab may be effective in patients who respond poorly to IV bisphosphonates (bisP)[1]
  - Similar ↓ in uNTx bone resorption BTM with and without previous IV bisP therapy[1]
    - uNTx decline in 9 days for Dmab in both bisP naïve and prior bisP treated patients
  - Better ↓ in TRAP BTM of osteoclast number than IV bisP (73% vs 11% decline)
- Superior effects of Dmab on bone[2] (vs ZOL) in time to 1st SRE (HR=.82), skeletal morbidity rate, ↓ in BTM,
  - DFS and OS – rates similar for Dmab and ZOL

DFS=disease free survival. OS=overall survival. BTM=bone turnover markers. ZOL=zoledronic acid. uNTX=urine amino terminal crosslink of type 1 collagen. TRAP=tartrate resistant acid phosphatase. HR=hazard ration. [1]J Bone Miner Res 2010;25:440. [2]J Clin Oncol 2010;28:5132.

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# Metastatic Cancer & Antiresorptive Therapy
## Safety and adverse effects (AE)

- Hypocalcemia
  - More frequent with Dmab (9.6%) vs ZOL (5%)[1]
- Renal function decline
  - ZOL with renal function ↓ in 10.7% of patients[2]
  - Dmab not renal excreted (limited studies with CrCl <30 mL/min)
- ONJ – after dental extraction, but may occur spontaneously (blood flow, bacteria, mastication and microfracture, duration of bisP Rx may all play a role)
  - Prevalence 1-10%; 50% ↓ with oral preventive care
  - ONJ ns between ZOL and Dmab after 3 yrs[3]

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Dmab=denosumab. ZOL=zoledronic acid. ONJ=osteonecrosis of he jaw. CrCl=creatinine clearance. bisP=bisphosphonate. [1]Eur J Cancer 2012;48:3082. [2]Cancer J 2001;7:377. [3]Ann Oncol 2012;23:1341.

 

# Antiresorptive Therapy & 'Drug Holidays'

## Effect on BMD & BCM during/after 2-yrs PMO Rx

| *Bauer DC. JBMR 2011; 26(2):239* | Alendronate, 5–10 mg/day[b] ($n = 437$)[13] | Risedronate, 5 mg/day ($n = 398$)[14] | Denosumab, 60 mg/6 month ($n = 128$)[15] |
|---|---|---|---|
| Effects on bone mass[c] | | | |
| 0- to 24-month change on active treatment | | | |
| Lumbar spine | 6.0%* | 5.0%* | 6.5%[d] |
| Femoral neck | 3.0%* | 2.0%* | NA |
| Total hip | 2.5%* | NA | 3.4%[d] |
| 12-month change after discontinuation[c] | | | |
| Lumbar spine | −1.3% | −0.8%** | −6.5%[d] |
| Femoral neck | −0.8% | −1.2%** | NA |
| Total hip | −1.3% | NA | −3.5%[d] |
| Effects on bone turnover[c] | | | |
| 0- to 24-month change on active treatment | | | |
| NTX | −65%* | −55%* | NA |
| sCTX | NA | NA | −65%* |
| PINP | NA | NA | −70%* |
| 12-month change after discontinuation | | | |
| NTX | 23%** | 67%** | NA |
| sCTX | NA | NA | 40%[d] |
| PINP | NA | NA | 40%[d] |

# Treatment of MAHC

## Adjuvant therapy

- Calcitonin
  - Weak antiresorptive effect, ↑es calcium excretion
    - Dose 50-200 units sq b.i.d.
  - Action within 1-2 days; effect transient (1-2 days)
    - May benefit while awaiting bisP onset of action
- Corticosteroids
  - Lymphoma 1,25-di$(OH)_2$D mediated hypercalcemia
    - ↓es GI vitamin-D mediated calcium absorption
  - Multiple myeloma and breast cancer
    - ↓es OC mediated bone resorption

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bisP=bisphosphonate. OC=osteoclast. MAHC=malignancy associated hypercalcemia. GI=gastrointestinal. OC=osteoclast. ECF=extracellular fluid.

 

# Treatment of MAHC
## Adjuvant therapy

- Plicamycin (mithramycin)
  - Chemotherapy agent inhibits OC RNA synthesis
    - Onset 12 hr, nadir 72 hr, duration days to wks
    - 15-25 mcg/kg IV over 4-6 hr, can repeat q24-48 hr
- Gallium nitrate
  - Adsorbs to and ↓es the solubility of hydroxyapatite crystals, ↓ing OC bone resorption
    - Onset slow, nadir 8 days
    - 200 mg/$m^2$ BSA per day over 5 days

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bisP=bisphosphonate. MAHC=malignancy associated hypercalcemia. BSA=body surface area. ECF=extracellular fluid. OC=osteoclast. RNA=ribonucleic acid.

 

## Patient Scenario – cont

- 23 y.o. woman admitted to hospital with stage IV metastatic melanoma to the lung and bones, with non-PTH mediated hypercalcemia
- Treatment & hospital course
  - IV fluid hydration + calcitonin Rx
    - Improved mental status
  - Zoledronic acid 4 mg IV, calcium normalized
    - PTHrP reported as 15 pmol/L (normal <2.0)
  - Denosumab initiated for recurrent hypercalcemia, and dismissed from hospital with normal serum calcium

# Conclusion – 1

## Antiresorptive Rx in bone metastases/hypercalcemia

- ASCO[1]
  - Suggests there is insufficient evidence to recommend a preference for ZOL vs Dmab
- ZOL has been viewed as the "standard bisphosphonate" for metastatic bone disease
  - ZOL with better pain control and greater ↓ in BTM than pamidronate and clodronate[2]
- Dmab more efficacious to ↓ SRE vs ZOL therapy

  *but*…ns in disease free survival or overall survival

  *and*…bone loss may ↑ rapidly after Dmab stopped

ASCO=American Society for Clinical Oncology. BTM=bone turnover markers. SRE=skeletal related events. Dmab=denosumab. ZOL=zoledronic acid. [1]J Clin Oncol 2011;29:1221. [2]J Clin Oncol 2006;24:4895. [3]Expert Rev Anticancer Ther 2012;12:307.

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# Conclusion – 2

## Antiresorptive Rx in bone metastases/hypercalcemia

- Decreases early bone loss from AI / ADT use
- Decreases overall burden of disease, and skeletal-related events (SRE) with improved QOL[1]
  - Dmab superior to ZOL to ↓ time to 1st SRE, ↓ frequency of SRE, ↓ bone pain, and ↓ SMR
- ASCO recommendations
  - Treatment as soon as metastatic disease is present (outcome data limited to <2 yrs)[2]
  - Treat hypercalcemia of malignancy
  - Drug therapy should be individualized to ↓ AE's

ASCO=American Society for Clinical Oncology. AE=adverse events. ADT=androgen deprivation therapy. AI=aromatase inhibitor. SMR=skeletal morbidity rate. QOL=quality of life. Dmab=denosumab. ZOL=zoledronic acid. [1]Expert Rev Anticancer Ther 2011;11:999. [2]J Clin Oncol 2011;29:1221.

MAYO CLINIC

 

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# Thank You !

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